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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/637,132	08/10/2000	John D. Baxter	UCAL-246/02/1US	9124

7590

04/22/2003

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EXAMINER

SMITH, CAROLYN L

ART UNIT

PAPER NUMBER

1631

DATE MAILED: 04/22/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/637,132

Applicant(s)

BAXTER ET AL.

Examiner

Carolyn L Smith

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 8/22/2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18,41,61 and 62 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18,41,61 and 62 is/are rejected.
- 7) ☒ Claim(s) 18,41,61 and 62 is/are objected to.
- 8) ☒ Claim(s) 18,41,61 and 62 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 August 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: See Continuation Sheet.

Continuation of Attachment(s) 6). Other: Petition granted (Paper No. 14).

DETAILED ACTION

Applicants' election of Specie D (Appendix 6: TR- α LBD-122/410 complexes with Triac) in Paper No. 13, filed on 1/13/03, is acknowledged. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The deletion of inventors in Paper No. 3, filed on 8/10/00, is acknowledged.

Claims 1-17, 19-40, and 42-60 were previously cancelled in Paper No. 3, filed 8/10/00.

The petition in Paper No. 2, filed on 8/10/00, which was filed under 37 CFR 1.84(a)(2) for colored photographs is granted permitting their use as drawings.

Claims herein under examination for this divisional application are claims 18 (amended), 41 (amended), 61, and 62.

Claim Objections

Claims 18 (line 12), 41 (line 13), 61 (line 11), and 62 (line 14) are objected to because of the following informality: The specification refers to the first appendix as "Appendix 1"; however, the Applicants refer to this appendix in the claims as "Appendix I". Applicants incorrectly refer to "I" in their claims which should be amended to coincide with the "1" as seen in the specification. Appropriate correction is required.

Claims Rejected Under 35 U.S.C. § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 18, 41, 61, and 62 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. While the invention is directed to modeling test compounds which is not apparently directed to selecting compounds which are found in nature, the modeled compounds in the claims include naturally occurring products of nature, particularly peptide compounds. The claims, as written, do not distinguish between peptides that naturally occur in organisms and bind to thyroid hormone receptors and those that are man-made.

Claim Rejections Under 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of the skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

LACK OF SCOPE OF ENABLEMENT

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Claims 18, 41, 61, and 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some test compounds such as Triac, does not reasonably provide enablement for where to obtain unspecified test compounds in an attempt to fit into the TR binding site. Although the said binding site is defined by the atomic coordinates, the number of molecules that are known to scientists is enormous. A narrowing of the selection of test compounds is needed to practically and predictably focus in to a "selective" modulator of TR activity in a reasonable amount of computation time. Such a narrowing, in fact, is already described in the specification via the Formula I type of molecule as discussed on page 10. However, the invention as presently stated in the claims does not include this narrowing guideline causes a lack of scope of enablement of the instant invention for one skilled in the art.

LACK OF ENABLEMENT

Claims 18, 41, 61, and 62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement of essential subject matter for the practice of claims cannot be properly supplied by the incorporation by reference of a publication. As claims 18, 41, 61, and 62 include the limitation that compounds are excluded as listed in a reference in Appendix 1, this is an improper incorporation by reference.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be

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accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claims Rejected Under 35 U.S.C. § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18, 41, 61, and 62 are rejected under 35 U.S.C. § second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claims 18 and 41, on lines 11 and 12, respectively, are vague and indefinite because of the phrase "said compound." It is unclear if the compound is referring to the originally mentioned peptide, peptidomimetic, peptidomatic, or synthetic compound or to the compounds being modeled which could be different from the afore-mentioned compounds. Appropriate correction is required.

Claim 18, lines 4 and 5, is vague and indefinite because of the phrase "fit spacially and preferentially." It is unclear which criteria the applicant is using for determining if and to what degree a compound fits or does not fit into the binding domain. Also, it is unclear what is meant by "preferentially," as it is relative terminology. Clarification of the metes and bounds of the instant claim is required.

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Claims 18 and 41 are vague and indefinite because of the phrases "selectively modulating" and "selectively modulates," on line 2 of each claim. It is unclear as "selectively modulating/modulates" has not been defined as to what is and is not selective. Clarification of the metes and bounds of this phrase via clearer claim wording is requested.

Claim 62, line 13, recites the phrase "said molecule" which lacks antecedent basis as molecule was not previously mentioned in the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18, 41, 61, and 62 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Evans et al. (P/N 5,298,429).

Evans et al. disclose Triac as a protein that binds to rTR- α as seen in hormone binding competition studies (col.82, lines 58-65). The ligand binding domain sequence region of rTR- α disclosed by Evans et al. falls within the region of the elected specie in the instant invention, LBD-122/410, as further described below. Evans et al. disclose the amino acid sequence (1-410) of the thyroid hormone receptor from a rat brain clone (col. 6, lines 54-57) in Figure VII-1(B)(a) to VII-1(B)(b). Evans et al. disclose the receptor protein in Figure VII-2 (col. 6, lines 58-62) with the hormone-binding domain listed between amino acids 194 to 410 (col. 84, lines 40-51). As the instant specification states the ligand binding domain will be less than 300 amino acids, preferably between 150 to 250 amino acids in length and spans amino acids 122 (Met) to 410 (Val) (page 24, lines 17-21), the ligand binding domain disclosed by Evans et al. meets this criteria. The rTR- α and Triac complex disclosed by Evans et al. and the claimed rTR- α and Triac complex of the instant invention are the same product and are not distinguishingly different, since the same molecules are binding together. It is not possible for the Examiner to physically compare the claimed rTR- α and Triac complex with the one reported by Evans et al.

Because the rTR- α and Triac complex is the same product in Evans et al. and the instant invention, the rTR- α and Triac complex of Evans et al. suggests that it would have the same

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properties as found in the instant invention, regardless of the methodology used to obtain the product.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second paragraph, first full paragraph).

Claim Rejections - 35 USC § 103

Claims 18, 41, 61, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al. (P/N 5,298,429), taken in view of Moore et al. (P/N 5,459,077) and Cramer, III et al. (P/N 5,307,287).

Evans et al. describe various proteins, including Triac (a non-thyronine-like compound), which were used in bioassays to determine binding affinity with a rat thyroid hormone receptor (rTR- α) compared to another receptor, rTR- β (col. 82, lines 47-65). See above 102/103 rejection regarding Evans et al.'s disclosure on the rTR- α ligand binding domain including a portion of the 122/410 sequence region that forms a complex with Triac. Evans et al. describe bioassays which determine whether a compound is a hormone receptor agonist or antagonist (abstract). Evans et al. describe a bioassay using data including variations in transcription levels as a function of test compound concentration which indicate the ability of the test compound to alter transcription activation (abstract). However, Evans et al. do not identify the compounds via

modeling compounds on a computerized system that fit into the TR ligand binding domain (TR LBD) or select compounds comprising conformationally constrained structures that interact with conformationally constrained residues of a TR LBD.

Moore et al. discuss methods of modeling the three-dimensional spatial (tertiary) structure (with known spatial assignments for each atom), designing, and synthesizing biologically active ligands and mimetics, such as antagonists and agonists, which can be peptides, nonpeptides, or synthetic (col.1, lines 13-17; col. 2, lines 39-49 and 66-67; and col. 6, lines 52-63). Moore et al. discuss creating three-dimensional models of antagonists and agonists to a biologically active receptor (col. 3, lines 23-26 and 51-54), taking into account three-dimensional conformational information (col. 3, 37-39 and 66-67) and identifying a compound having a three-dimensional structure sufficiently similar to the ligand, so that it is complementary to the receptor (col. 3, lines 46-48 and col. 4, lines 8-10). Moore et al. mention specific examples of "biologically active molecules... and the like" (col. 8, lines 16-24), which include thyroid hormone receptors. Although the atomic structure points are different from the instant invention, it would have been obvious to one with skill in the art to use different structure points that pertain any receptor of interest, as Moore et al. state that their model could be used to model the three-dimensional spatial structure of biologically active ligands complementary to a receptor (col. 3, lines 23-27 and 51-54) which, by definition, includes thyroid hormone receptors.

Cramer, III et al. describe a computer-implemented methodology of using three-dimensional graphics and statistical techniques to correlate shapes of molecules with their biological properties (abstract). Cramer, III et al. describe how calculations of spatial coordinates are derived for a molecule (abstract). Cramer, III et al. discuss how further analysis

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of these data result in a three-dimensional display for visualization and understanding of intermolecular interactions as well as predictions in biological activity (abstract). Cramer, III et al. point out that one must obtain information on the three-dimensional shape of molecules if one wants to better describe and understand the functioning of biological macromolecules, including target receptor molecules (col. 1, lines 39-43 and lines 57-62).

Evans et al. point out that receptors made available from their invention can then be described in detailed structural analyses by using X-ray diffraction methods to analyze receptor crystals (col. 87, lines 41-52). Due to the slow process of obtaining X-ray crystallographic structures to obtain three-dimensional stereo confirmation of biomolecules, as stated by Cramer, III et al. (col. 2, lines 3-7 and 46-50), a skilled artisan (researcher) would have been motivated to improve techniques for obtaining this information. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to enhance receptor binding studies, like those by Evans et al., by adding the computerized three-dimensional work of Cramer, III et al. and Moore et al., followed by the bioassays used by Moore et al., because the contemporary improvements at the time would allow one to characterize molecules interacting with receptors (Evans et al., col. 87, lines 44-52). Thus, Evans et al., in view of Moore et al. and Cramer, III et al., motivate the instant invention.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the

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Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (703) 308-6043. The examiner can normally be reached Monday through Friday from 8 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

April 7, 2003


ARDIN H. MARSCHEL
PRIMARY EXAMINER